CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-785

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA
Division of Anti-infective Drug Products, HFD-520

NDA number: 50-785 (000)

KEY WORDS: Augmentin, amoxicillin, clavulanate

Reviewer Name: Kenneth Seethaler, R.Ph., Ph.D., D.A.B.T.

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Review completion date: January 23, 2001

Scientific literature reviewed: Yes ( ) No (x)

Information to sponsor: Yes ( ) No (x)

Sponsor: SmithKline Beecham Pharmaceuticals
One Franklin Plaza
Philadelphia, PA 19101

Contact person: Cynthia D'Ambrosio, Ph.D.
Associate Director, U. S. Regulatory Affairs
Phone 215-751-3468

Drug: Augmentin — Tablets

INTRODUCTION

Augmentin — is a combination product consisting of the antibiotic amoxicillin, and the beta-lactamase inhibitor clavulanate potassium. Tablet, chewable tablet, and powder for oral suspension formulations of Augmentin are currently marketed in this country, [redacted] The extra-strength tablets described in this NDA, will each contain 1000 mg of amoxicillin and 62.5 mg of clavulanate.

The preclinical safety issues relevant to this NDA are the same issues that were addressed in an [redacted] Those issues deal with the fact that the new manufacturing process for amoxicillin, results in the introduction of some new impurities and residual solvents into the drug substance. The impurities are [redacted] and [redacted] of which are metabolized to inactive substances. The residual solvents are [redacted] all of which are present in less than toxic amounts.

The current NDA contained a report of one toxicology study that compared the toxicity of amoxicillin produced by the old and new manufacturing processes.

TOXICOLOGY

A Two-week Intravenous Toxicity Comparison Study in Rats

This was a GLP study conducted by the sponsor in England, that was designed to compare the toxicity of amoxicillins produced by two different manufacturing processes. The two types of amoxicillin were identified as [redacted] amoxicillin [redacted] produced by the [redacted] and [redacted] amoxicillin [redacted] produced by a newer [redacted]

In this study, groups of Sprague-Dawley rats (10/sex/group) received daily intravenous injections of either normal saline, [redacted] 250 mg/kg/day, [redacted] 500 mg/kg/day, or [redacted] 500 mg/kg/day for 14 days. Evaluations were based on observations, body weights, food and water consumption, hematology, serum chemistry, urinalysis, organ weights, and gross and microscopic histopathology.

Signs of renal toxicity were seen in about 10-20% of the animals in both of the 500 mg/kg/day groups. These signs were increases in plasma creatinine and urea, increased relative kidney weights, and degeneration and regeneration of renal tubule epithelium. Little or no toxicity was seen in the 250 mg/kg/day group. It was concluded that both types of amoxicillin produced similar toxicity.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATIONS

There are no outstanding safety concerns with the marketed amoxicillin produced by the original process, and based on the results of the comparison toxicology study, it does not appear that amoxicillin produced by the new process should generate any new safety concerns.

The text of the proposed label has been reviewed. The comparisons between the animal doses, and the human dose are based on body surface area. The label is considered to be acceptable as written.

From the Pharmacology/Toxicology perspective, there is no objection to the approval of this NDA.

Kenneth Seethaler, R.Ph., Ph.D., D.A.B.T.
Pharmacologist/Toxicologist, HFD-520

cc: Original NDA 50-785
HFD-104
HFD-340
HFD-520
HFD-520/Pharm/K. Seethaler
HFD-520/MO/C. Cooper
HFD-520/Micro/S. Altaie
HFD-520/Chem/S. Pagay
HFD-520/CSO/S. Samanta
HFD-520/Biopharm/J. Zheng
HFD-520/Biostat/T. Lin

Concurrence only:

HFD-520/R. Osterberg

HFD-520/L. Gavrilovich

APPEARS THIS WAY
ON ORIGINAL

/s/

Kenneth Seethaler
1/30/01 12:01:11 PM
PHARMACOLOGIST

Robert Osterberg
2/1/01 07:20:39 AM
PHARMACOLOGIST

Lillian Gavrilovich
2/2/01 12:19:01 PM
MEDICAL OFFICER

Susmita Samanta
2/5/01 09:21:47 AM
CSO

APPEARS THIS WAY
ON ORIGINAL